water, and dried. A solution of 3.84 g (0.0174 mol) of trimethylsulfoxonium iodide in 75 mL of DMSO was combined with 566 mg (0.013 mol) of sodium hydride (55% oil suspension) and agitated for 1 h at room temperature. To this solution was added the dried crude tosylation product dissolved in 2 mL of DMSO dropwise. The reaction mixture was stirred for 30 min and precipitated into ice water. The resultant crude product was chromatographed on silica gel, thus producing 985 mg (48%) of 13: mp 214 °C; UV ϵ_{247} = 13 500.

6,6-Ethylene-18-methyl-15β,16β-methylene-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone (14). Under the above described conditions 372 mg (0.001 mol) of 18 was transformed to 145 mg (39%) of 14: mp 165 °C; UV ϵ_{242} = 14 700.

Method C. 6,6-Ethylene-15β,16β-methylene-3-oxo-17α-pregna-1,4-diene-21,17-carbolactone (16). A solution of 670 mg (0.0018 mol) of 12 and 670 mg (0.003 mol) of DDQ in 13.6 mL of toluene was stirred for 5 h at 100 °C. The reaction solution was then diluted with ether, washed with water sodium bicarbonate solution and water, dried, and evaporated. The residue was then chromatographed on silica gel. After recrystallization from diisopropyl ether/acetone, 445 mg (67%) of 16 was obtained: mp 200 °C; UV ϵ_{243} = 15 200.

6,6-Ethylene-15α,16α-methylene-3-oxo-17α-pregna-1,4-diene-21,17-carbolactone (15). Under the above-described conditions, 600 mg (0.0016 mol) of 11 was transformed to 520 mg (87%) of 15 as an oil: UV ϵ_{243} = 14 600.

Registry No. 3, 67372-62-7; 4, 67372-68-3; 5, 101765-54-2; 6, 101765-39-3; 7, 101834-16-6; 8, 84529-99-7; 9, 133753-23-8; 10, 133753-24-9; 11, 101834-17-7; 12, 101765-35-9; 13, 101765-58-6; 14, 133753-25-0; 15, 101834-18-8; 16, 101765-36-0; formalin, 50-00-0; aldosterone, 52-39-1.

Synthesis and Evaluation of Antiinflammatory Activities of a Series of Corticosteroid 17α-Esters Containing a Functional Group

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A series of 21-desoxy-21-chlorocorticosteroids that contain a functionalized ester group at 17α has been prepared and examined to separate their systemic activity from topical antiinflammatory activity. Introduction of the functionalized ester group at 17α was carried out by an acid-catalyzed formation of cyclic ortho esters with 17α,21-hydroxyl groups of corticosteroids and subsequent acid-catalyzed hydrolysis. As for the functional group, chloro, methoxy, acetoxy, cyano, cyclopropyl, or alkoxycarbonyl group was introduced at the terminal carbon atom of the 17α-alkanoate group. The topical antiinflammatory activity and systemic activity of these compounds were examined and found to be significantly dependent on the functionalities in the 17α-esters. Among these derivatives, a series of 17α-(alkoxycarbonyl)alkanoates (17α-OCO$(CH_2)_n$COOR) showed an excellent separation of the systemic activity from topical activity. The effects of the number of methylene groups (n) and of the alkyl groups of the ester (R) on either topical or systemic activity of the corticosteroid derivatives were also investigated.

Introduction

Since hydrocortisone was introduced into dermatological use,[1] many structural modifications of the hydrocortisone molecule have been made with the aim at enhancing antiinflammatory potency. Important structural modifications include halogenation,[2] methylation,[3] and introduction of a double bond at C-1 position of the steroidal skeletons.[4]

Also, it is confirmed that esterification of the 17α- and/or 21-hydroxyl groups[5] and replacement of the 21-hydroxyl group with a halogen atom[6] enhance the topical antiinflammatory activity due to improved penetration of the skin and to increased affinity for the glucocorticoid receptor.[7]

As a result of these modifications, 21-chloro-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17α-propionate (clobetasol propionate, CP) is found to have the strongest topical antiinflammatory activity in clinical use.[8] On the other hand, CP also shows severe adverse effects such as thymolysis and dermal atrophy.[8]

In the field of glucocorticoids, little success has been achieved in completely separating undesired side effects from topical antiinflammatory activity except for 21-carboxylate[9] and 17β-carboxylate[10] derivatives. However, the antiinflammatory activity of neither derivatives is as strong as that of CP. Teutsch et al.[11] and Kertesz and

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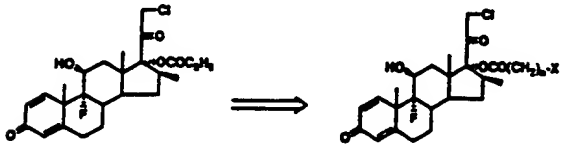
...arx[12] have reported some success in separating topical from systemic activity in glucocorticoids. Recently, Lee et al. also have reported the preparation of a new class of steroidal 16-esters and amides that are designed on the basis of the "antedrug" concept[13] defined as a chemically modified compound which exerts desirable effects at the local tissue, and rapidly decomposes into inactive compounds when it enters into metabolic circulation.

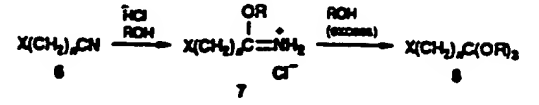


Clobetasol propionate (CP) Antedrug

Since the 17α-ester of glucocorticoids resists metabolic hydrolysis, it is expected that the ester can appropriately be modified with a terminal functional group so as to undergo metabolic inactivation prior to hydrolytic cleavage of the ester bond, and hence such glucocorticoids may not exhibit systemic adverse effects and provide good separation of local to systemic activities. To date, simple aliphatic carboxylate, benzoate,[14] carbonate,[15] and heterocyclic aromatic carboxylate[16] have been reported as esters of the 17α-hydroxyl group. Recently, Mitsukuchi et al. reported the synthesis of 17α-succinate derivatives of glucocorticoids.[17]

We have also attempted to separate the systemic adverse effects, such as adrenal suppressive effect and thymolysis, from topical antiinflammatory activity of glucocorticoid by modification of 17α-ester of glucocorticoids. We describe herein the synthesis of a series of 21-desoxy-21-chlorocorticosteroids with functionalized ester group at 17α and their remarkable ability to separate systemic effects from topical antiinflammatory activity.

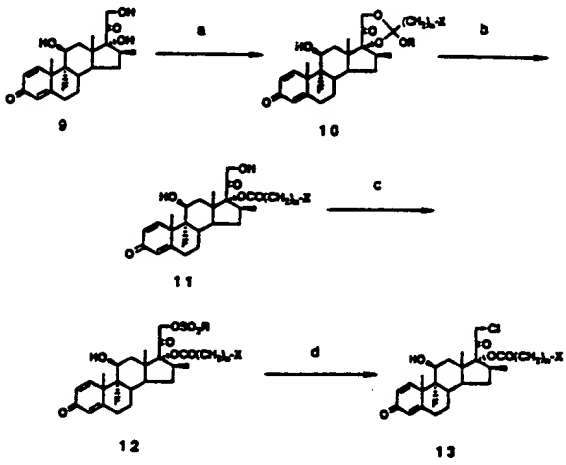
Table I. Preparation of Functionalized Ortho Esters



no.	X	n	R	yield 7 (%)	yield 8 (%)	bp 8 (°C/mmHg)
8a	OMe	1	Et	89	57	87–92/32
8b	OMe	2	Me	87	80	a
8c	Cl	1	Et	95	58	60–68/10
8d	Cl	3	Me	70	72	87–88/16
8e	OAc	2	Me	76	62	a
8f	SMe	1	Me	78	84	93–95/24
8g	CN	1	Me	90	75	78–80/6.0
8h	CN	2	Me	89	65	59–61/2.5
8i	cyclopropyl	0	Me	97	42	52–56/24
8j	cyclopropyl	1	Et	82	39	86–92/18
8k	CO_2Me	1	Me	77	56	73–75/6.0
8l	CO_2Me	2	Me	97	90	88–89/6.0
8o	CO_2Et	3	Et	92	57	125–128/10
8p	CO_2iPr[b]	2	Me		73	109–111/12
8q	CO_2tBu[b]	2	Me		64	104–106/12

[a] These ortho esters were used for the preparation of steroidal derivatives without further purification by distillation. [b] These ortho esters were prepared by alcohol exchange reaction of 8l (See the Experimental Section).

Scheme I[a]



[a] (a) X-$(CH_2)_nC(OR)_3$, *p*-TsOH, THF; (b) $AlCl_3$(aq), MeOH; (c) CH_3SO_2Cl, py or $(CF_3SO_2)_2O$, py, CH_2Cl_2; (d) LiCl, DMF.

Chemistry

Introduction of functionalized ester groups at 17α required the preparation of the respective functionalized ortho esters.

Preparation of Ortho Esters Containing a Functional Group. Ortho esters containing a functional group were prepared by a two-step synthesis using the corresponding nitriles as the starting materials, known as the Pinner synthesis.[18] The first step is the preparation of an imidate hydrochloride by the reaction of a nitrile with an alcohol and anhydrous HCl. The second step is the

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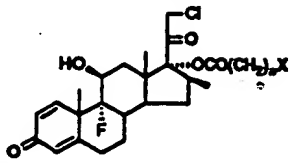
Table II. 21-Desoxy-21-chlorobetamethasone 17α-Functionalized Alkanoates



no.	X	n	mp (°C)	yield (%)	formula	anal.	edema[c] inhibn	thymolysis[c]	RA[d]
CP[a]							1	1	1
BMDP[b]							0.10	0.03	3.3
13a	OMe	1	209–210	41	$C_{26}H_{33}ClFO_6$	C, H, Cl	0.11	ND	ND
13b	OMe	2	194–195	63	$C_{28}H_{36}ClFO_6$	C, H, Cl	0.38	0.05	7.6
13c	Cl	1	207–210	44	$C_{26}H_{32}Cl_2FO_5$	C, H, Cl	0.25	ND	ND
13d	Cl	3	e	76	$C_{28}H_{36}Cl_2FO_5$	C, H, Cl	0.66	0.12	5.5
13e	OAc	2	177–179	64	$C_{27}H_{34}ClFO_7$	C, H, Cl	0.28	0.015	18.6
13f	SMe	1	204–205	65	$C_{25}H_{33}ClFO_5S$	C, H, Cl, S	0.35	0.35	1.0
13h	CN	2	e	43	$C_{28}H_{31}ClFNO_5$	C, H, Cl, N	0.07	ND	ND
13i	cyclopropyl	0	209–211	45	$C_{28}H_{32}ClFO_5$	C, H, Cl	0.44	1.3	0.34
13j	cyclopropyl	1	197–200	11	$C_{27}H_{34}ClFO_5$	C, H, Cl	0.51	1.1	0.46
13l	CO_2Me	2	215–216	60	$C_{27}H_{34}ClFO_7$	C, H, Cl	1.3	<0.01[f]	>130

[a] Clobetasol 17-propionate. [b] Betamethasone 17,21-dipropionate. [c] Potencies relative to clobetasol propionate (CP = 1). [d] Ratio of topical (edema inhibition) to systemic (thymolysis) activities. [e] Obtained as an amorphous product. [f] Granuloma inhibition or thymolitic activity was not detected at doses up to 100 μg/pouch. ND = Not determined.

alcoholysis of the imidate hydrochloride to the ortho ester. The preparation of imidate hydrochloride and alcoholysis to the ortho ester were usually carried out separately.

Attempts to prepare 3-chloroorthopropionate showed poor results. Methanolysis of 3-chloropropioimidate hydrochloride, which was made from 3-chloropropionitrile gave methyl 3-methoxypropionate as the predominant product. (The results are listed in Table I.)

Preparation of the Derivatives of 21-Desoxy-21-chlorobetamethasone 17α-Functionalized Alkanoates. The general method for the preparation of 21-desoxy-21-chlorobetamethasone 17α-functionalized alkanoates is depicted in Scheme I.

Commercially available β-methasone (9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione, 9) was used as a starting material. Esterification of the 17α-hydroxy group was carried out via the procedure of Ercoli et al.[19] Treatment of β-methasone (9) with the functionalized ortho esters 8, preparation of which were described above, and *p*-toluenesulfonic acid as an acid catalyst at ambient temperature gave cyclic ortho esters 10. The ortho esters thus obtained were hydrolyzed in the presence of $AlCl_3$ in aqueous MeOH to give 21-hydroxy-17α-alkanoates (11).

Certain cyclic ortho esters, 10g and 10k, could not be obtained from the corresponding cyanoorthoacetate 8g and (methoxycarbonyl)orthoacetate 8k, because under acidic conditions, the ortho acetate possessing an electron-withdrawing group, such as a carbonyl or nitrile group, at the α-position decomposed.

Transformation of 21-hydroxy-17α-alkanoates (11) into 21-chloro derivatives (13) was accomplished as follows: The 21-hydroxy group was transformed into an appropriate leaving group such as a mesylate or triflate. The crude 21-sulfonates without further purification were readily treated with LiCl in DMF to give the 21-desoxy-21-chloro derivatives (13).

Preparation of 13m and 13n was carried out via alcohol exchange reaction of 13l and 13o, respectively, under basic conditions. The results are summarized in Table II.

Biological Results and Discussion

Topical antiinflammatory activity was measured in mice by a modification of the croton oil ear assay of Tonelli et al.[20] and thymolytic activity was determined in the rat granuloma pouch assay system.[21] For the evaluation of topical antiinflammatory activity of corticosteroids, the croton oil ear assay shows good correlation to clinical potency compared to granuloma pouch assay. On the other hand, the granuloma pouch assay reflects systemic effects of corticosteroids such as thymolysis rather than topical activities.[20] Table III shows the topical antiinflammatory activity and the potency of thymolysis of 21-chloro-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17α-functionalized alkanoates relative to CP. For comparison, the data for betamethasone 17α,21-dipropionate (BMDP) are also listed.

In a preliminary study, several kinds of functional groups such as methoxy, chloro, acetoxy, methylthio, cyano, cyclopropyl, and methoxycarbonyl were introduced on an ω-position in the 17α-ester group. The number of methylene groups was altered from one to three. Topical antiinflammatory activity, thymolytic activity, and the ratio of topical to systemic activity (RA) of these compounds are shown in Table II. The topical antiinflammatory activity of the parent compound (CP) was weakened by introduction of any functional group to the 17α-ester except for the methoxycarbonyl group (13l), whereas, thymolytic activity varied with each functional group.

Functionalization with methoxy, acetoxy, and chloro groups resulted in weakening of the thymolytic activity. Compounds 13b (17α-$OCO(CH_2)_2OMe$), 13d (17α-$OCO(CH_2)_3Cl$), and 13e (17α-$OCO(CH_2)_2OAc$) showed good separation of topical antiinflammatory activity from thymolytic activity. (13b, RA = 7.6; 13d, RA = 5.5; 13e, RA = 18.6.) On the other hand, the derivatives of methylthio and cyclopropyl groups exhibited low separation of thymolytic activity. (13f, 17α-$OCOCH_2SMe$, RA = 1.0; 13i, 17α-$OCOC_3H_5$, RA = 0.34; and 13j, 17α-$OCOCH_2C_3H_5$, RA = 0.46.) Especially, both cyclopropyl derivatives, 13i and

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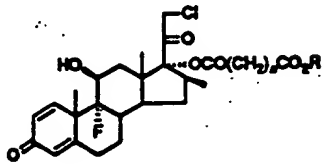
Table III. 21-Desoxy-21-chloro-β-methasone-17α-dicarboxylic Acid Esters



no.	R	n	mp (°C)	yield (%)	formula	anal.	edema[a] inhibn	thymolysis[a]	G–R binding (IC_{50}, nM)
CP[c]							1	1	3.17
BMDP[d]							0.10	0.03	5.25
13l	Me	2	215–216	60	$C_{25}H_{34}ClFO_7$	C, H, Cl	1.30	–[f]	5.18
13m	Me	3	251–254	62[e]	$C_{26}H_{36}ClFO_7$	C, H, Cl	0.45	–[f]	ND
13n	Et	2	228–230	57[e]	$C_{26}H_{36}ClFO_7$	C, H, Cl	0.56	–[f]	ND
13o	Et	3	d	89	$C_{27}H_{38}ClFO_7$	C, H, Cl	0.68	–[f]	9.68
13p	i-Pr	2	163–164	91	$C_{27}H_{38}ClFO_7$	C, H, Cl	0.11	–[f]	12.1
13q	t-Bu	2	167–168	89	$C_{28}H_{40}ClFO_7$	C, H, Cl	0.19	–[f]	10.8
13r	H	2	d	92[g]	$C_{23}H_{30}ClFO_7$	C, H, Cl	<0.01[h]	–[f]	>150

[a] Clobetasol 17-propionate. [b] Betamethasone 17,21-dipropionate. [c] Potencies relative to clobetasol propionate (CP = 1). [d] Obtained as an amorphous product. [e] These compounds were prepared by alcoholysis of 13m with methanol and 13l with ethanol, respectively (see the Experimental Section). [f] Obtained by hydrolysis of 13l in an acidic condition (see the Experimental Section). [g] Thymolysis was not detected at doses up to 100 μg/pouch. [h] Edema inhibition was not detected at doses up to 3.0 μg/mL. ND = Not determined.

13j showed stronger thymolytic activity compared to topical activity, and their thymolytic activities were equal to that of CP (13i, 1.3-fold; 13j, 1.1-fold). These compounds may resist inactivation through the metabolic pathway.

In contrast to the compounds described above, the methoxycarbonyl group (13l) showed as potent topical antiinflammatory activity as CP (1.3-fold). Moreover, the thymolytic activity of 13l was dramatically reduced to afford excellent separation of systemic thymus involution from topical antiinflammatory activity (RA > 130).

The results obtained from the above investigations suggested that three structural features of the 17α-ester group affect the topical antiinflammatory and the thymolytic activity of glucocorticoids. (1) The 17α-esters containing a functional group that is rapidly transformed into a hydrophilic functional group through metabolism in circulation exhibit good separation of topical antiinflammatory to systemic activity. (2) Compounds that have a 17α-ester containing a hydrophobic functional group such as alkyl, chloro, and methylthio retain systemic activity and exhibit poor separation. (3) Bulkiness of the 17α-ester group is also an important property. There might be an optimal volume for the 17α-ester at the binding site of the receptor.

Based on the preliminary studies described above, further investigations were focused on the 21-desoxy-21-chlorobetamethasone derivatives of 17α-dicarboxylic acid esters. For the purpose of optimization, the number of methylene groups (n) and the alkyl group (R) of the ester were varied and the topical antiinflammatory activity, thymolytic activity, and binding ability to glucocorticoid receptor of these derivatives were examined (Table III).

As for the variation of the number of methylene group (n), 17α-succinate (n = 2) and 17α-glutarate (n = 3) were examined. Methyl succinate (13l) showed stronger topical antiinflammatory activity than methyl glutarate (13m), and ethyl succinate (13n) and ethyl glutarate (13o) showed the same topical activity. None of these compounds showed detectable thymolysis.

The terminal alkyl group (R) also affected on the biological activities of the corticosteroid derivatives of 17α-dicarboxylic acid esters. Both the topical activity and binding affinity with glucocorticoid receptor were decreased in the order of Me (13l), t-Bu (13q), and i-Pr (13p). In the series of the derivatives of dicarboxylic acid esters, the topical antiinflammatory activity and the affinity with glucocorticoid receptor showed good correlation. On the contrary, thymolytic activity was drastically weak compared to those of CP in both series of 17α-succinates and 17α-glutarates. Only *tert*-butyl succinate (13q) showed moderate granuloma inhibition (0.12-fold of CP), but no thymic involution was observed.

In order to investigate the difference of species, the systemic effects of CP and 13l were evaluated in infant mice. Ethanol solution of drugs were daily applied to the ear of infant male mice for 7 days. On the eighth day, the mice were killed and the thymus was removed and weighed. Though CP showed thymolysis at 0.1 mg/kg (sc), 13l showed no thymolysis at dose up to 10 mg/kg (sc). This result was consistent with the result that was observed in the rat granuloma pouch assay (data not shown).

In order to elucidate high separation of systemic activity from topical activity in a series of 17α-dicarboxylic acid esters, preliminary metabolic studies of analogues of 17α-succinate esters 13l (Me), 13p (i-Pr), and 13q (t-Bu) were carried out.

Each steroid was dissolved in MeOH at a concentration of 2.0 mM, and 50 μL of each MeOH solution was added to 1.0 mL of human skin homogenate (5 mg of protein/mL) and incubated at 37 °C for 1 h. The incubation mixture was extracted with 3.0 mL of EtOAc, and the organic layer was separated and evaporated. The residue was analyzed by reverse-phase HPLC. From the incubation mixture of 13l, the free acid 13r was detected as a predominant metabolite. On the contrary, 13r was scarcely detected from the incubation mixture of 13p and 13q (data not shown).

For evaluation of the biological activities of the main metabolite, the free acid 13r was synthesized by hydrolysis of methyl succinate (13l) under acidic condition. The main metabolite 13r showed little binding with glucocorticoid receptor up to a concentration of 150 nM and showed neither topical antiinflammatory activity nor thymolytic activity. (The data are shown in Table III.)

These results suggest that the ester of the primary alcohol (COOR = COOMe) is rapidly hydrolyzed to free acid 13r as an inactive metabolite in the local metabolism. On the other hand, the ester of the tertiary alcohol (COOR = COOtBu) resists local metabolic hydrolysis to show

...derate granuloma inhibition activity but is inactivated through systemic metabolism, especially through hepatic metabolism, to show undetectable thymolysis. The ester of the secondary alcohol (COOR = COOiPr) exhibited moderate metabolic behavior. Though the compound 13p resisted metabolic hydrolysis in the human skin homogenate in vitro, it showed neither granuloma inhibition nor thymolysis.

In summary, introduction of (alkoxycarbonyl)alkanoate esters to the 17α-hydroxy group in corticosteroids could be an excellent method to provide an "antedrug" which shows high separation of topical antiinflammatory activity from systemic adverse effects of corticosteroids.

Experimental Section

All melting points were determined in open capillary tubes on Mettler FP61 and were uncorrected. Elemental analyses were performed by a Perkin-Elmer 240-C elemental analyzer. IR spectra were determined by a JASCO infrared spectrophotometer. ^{1}H NMR spectra were determined on a Varian HA-100 or a JEOL JMN-PS-100 spectrometer at ambient temperature in $CDCl_3$ or DMSO-d_6 with TMS used as an internal standard. Chemical shifts are given in δ (ppm). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; qu, quintet; m, multiplet; br, broad. Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck, F-254). Silica gel for column chromatography was purchased from Wako Pure Chemical Co., WAKO-Gel C-300, 200–300 mesh.

Preparation of Ortho Esters Containing a Functional Group. Two typical procedures for preparing trimethyl 3-(methoxycarbonyl)orthopropionate (8l) and triethyl methoxyorthoacetate (8a) were as follows.

Trimethyl 3-(Methoxycarbonyl)orthopropionate (8l). Into an ice-cooled solution of 3-(methoxycarbonyl)propionitrile (54.0 g, 0.48 mmol) and anhydrous MeOH (21.3 mL, 0.53 mmol) in anhydrous ether (350 mL) was bubbled HCl(g) until saturation (ca. 9 equiv of HCl was absorbed). After the resulting solution was allowed to stand at 0 °C for 24 h, the solvent and excess HCl were removed under reduced pressure at ambient temperature to give a white salt. The salt was successively washed with anhydrous ether and dried under reduced pressure to give methyl 3-(methoxycarbonyl)propioimidate hydrochloride (7l) (84.1 g, 97% yield). The imidate salt was dissolved in anhydrous MeOH, and the solution was stirred at room temperature for 26 h. As the reaction proceeded, NH_4Cl precipitated. After the salt was filtered off, the filtrate was diluted with ether. The ethereal solution was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Filtration and evaporation afforded the crude product (86.9 g), which was distilled to give trimethyl 3-(methoxycarbonyl)-orthopropionate (8l) (83.5 g, 90% yield): bp 88–89 °C (6.0 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.82–2.51 (m, 4 H), 3.20 (s, 9 H), 3.67 (s, 3 H).

Triethyl Methoxyorthoacetate (8a). Following the procedure described above, methoxyacetonitrile (9.56 g, 0.13 mmol) was treated with anhydrous EtOH and HCl(g) to give ethyl methoxyacetoimidate hydrochloride (7a) (18.7 g, 89% yield), which was subjected to alcoholysis with anhydrous EtOH to afford, after distillation, triethyl methoxyorthoacetate (8a) (13.1 g, 57% yield): bp 87–92 °C (32 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7.0 Hz), 3.36 (s, 3 H), 3.47 (s, 2 H), 3.58 (q, 2 H, J = 7.0 Hz).

Other ortho esters except 8p and 8q were prepared similarly using the corresponding nitriles (0.02–0.45-mol scale). All results are given in Table I.

Trimethyl 3-(Isopropoxycarbonyl)orthopropionate (8p). Sodium chips (500 mg, 21.7 mmol) were added into 200 mL of 2-propanol, and the mixture was stirred at ambient temperature for 2 h. After the sodium chips were completely dissolved, 10.0 g (52 mmol) of trimethyl 3-(methoxycarbonyl)orthopropionate (8l) was added. Stirring was continued at 55 °C for 1.5 h, and the resulting mixture was diluted with ether. The ethereal solution was washed with aqueous NH_4Cl and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation afforded 12.3 g of an oily crude product, which was distilled under reduced pressure to give 8.40 g of trimethyl 3-(isopropoxycarbonyl)orthopropionate (8p) (73% yield): bp 109–111 °C (12 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 6 H, J = 6.0 Hz), 2.00–2.07 (m, 2 H), 2.25–2.31 (m, 2 H), 3.20 (s, 9 H), 4.96 (qu, 1 H, J = 6.3 Hz).

Trimethyl 3-(*tert*-Butyloxycarbonyl)orthopropionate (8q). Into a solution of 10.0 g (52.0 mmol) of trimethyl 3-(methoxycarbonyl)orthopropionate (8l) in 200 mL of *tert*-butyl alcohol was added 4.80 g (42.8 mmol) of t-BuOK. Stirring was continued at 60 °C for 24 h, and the reaction mixture was cooled to room temperature and diluted with ether. The ethereal solution was washed with aqueous NH_4Cl and brine and dried over $MgSO_4$. Filtration and evaporation afforded 11.4 g of an oily crude product, which was distilled under reduced pressure to give 7.75 g of trimethyl 3-(*tert*-butyloxycarbonyl)orthopropionate (8q) (64% yield): bp 104–106 °C (12 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.97–2.04 (m, 2 H), 2.20–2.27 (m, 2 H), 3.20 (s, 9 H).

Preparation of the Derivatives of 21-Desoxy-21-chlorobetamethasone 17α-Functionalized Alkanoates. A typical procedure for preparing 21-chloro-9α-fluoro-11β-hydroxy-17α-((3-(methoxycarbonyl)propanoyl)oxy)-16β-methylpregna-1,4-diene-3,20-dione (13l) was as follows:

9α-Fluoro-11β,21-dihydroxy-17α-((3-(methoxycarbonyl)-propanoyl)oxy)-16β-methylpregna-1,4-diene-3,20-dione (11l). Into a mixture of 15.0 g (38.2 mmol) of 9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (betamethasone) and 14.7 g (76.4 mmol) of trimethyl 3-(methoxycarbonyl)orthopropionate (8l) in 75 mL of THF was added 0.5 g of *p*-toluenesulfonic acid. After being stirred at ambient temperature for 12 h under nitrogen, the reaction mixture was treated with 2 mL of Et_3N. The resulting solution was poured into aqueous $NaHCO_3$ and extracted with EtOAc. The organic extracts were washed with brine and dried over anhydrous $MgSO_4$. Filtration and evaporation under reduced pressure gave 16.0 g of the crude ortho ester (10l).

A solution of crude 10l and 60 mL of 0.28% aqueous $AlCl_3$ in 200 mL of MeOH was stirred at ambient temperature for 8 h. The reaction mixture was treated with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were washed with brine and dried over anhydrous $MgSO_4$. Filtration and evaporation under reduced pressure gave the crude product, which was chromatographed on silica gel to afford 15.0 g of 11l (81% yield).

21-Chloro-9α-fluoro-11β-hydroxy-17α-((3-(methoxycarbonyl)propanoyl)oxy)-16β-methylpregna-1,4-diene-3,20-dione (13l). Into a mixture of 15.0 g (29.6 mmol) of 11l and 31 mL of Et_3N in 300 mL of CH_2Cl_2 was added 5.10 g (44.4 mmol) of methanesulfonyl chloride dropwise at 0 °C. Stirring was continued at 0 °C under nitrogen for 30 min. The reaction mixture was poured into ice-cooled 3 N HCl and extracted with CH_2Cl_2. The extracts were washed with aqueous $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation under reduced pressure gave 20.6 g of the crude mesylate (12l).

A mixture of crude 12l and 6.28 g (148 mmol) of LiCl in 190 mL of DMF was stirred at 90 °C under nitrogen for 5 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc. The organic solution was washed with brine three times and dried over anhydrous $MgSO_4$. Filtration and evaporation under reduced pressure gave the crude product, which was chromatographed on silica gel. Recrystallization from EtOAc and *n*-hexane gave 11.7 g of 13l (75% yield): mp 215–216 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 1.28 (d, 3 H, J = 6.0 Hz), 1.51 (s, 3 H), 3.58 (s, 3 H), 4.21 (s, 2 H), 5.30–5.48 (m, 1 H), 6.04 (d, 1 H), 6.24 (dd, 1 H, J = 10 Hz, J = 2.0 Hz), 7.30 (d, 1 H, J = 10 Hz); IR (KBr) 3450, 1735, 1665, 1635, 1620, 1610 cm^{-1}. Anal. ($C_{32}H_{34}ClFO_7$) C, H, Cl.

Other derivatives of 21-desoxy-21-chlorobetamethasone 17α-functionalized alkanoate except 13m, 13n, 13p, and 13q were similarly prepared from betamethasone using the corresponding ortho esters above prepared. All results are given in Tables II and III.

9α-Fluoro-11β,21-dihydroxy-16β-methyl-17α-((3-(isopropoxycarbonyl)propanoyl)oxy)pregna-1,4-diene-3,20-dione (11p). Compound 11p was obtained by the similar procedure described for compound 11l. Betamethasone (0.80 g, 2.04 mmol) and the ortho ester 8p (0.81 g, 3.67 mmol) gave 10p, which was converted to 1.30 g of crude 11p. The crude 11p was used in the next step without further purification.

21-Chloro-9α-fluoro-11β-hydroxy-16β-methyl-17α-((3-(isopropoxycarbonyl)propanoyl)oxy)pregna-1,4-diene-3,20-dione

(13p). Into a solution of 1.02 g of the crude 11p and 0.70 mL of pyridine in 20 mL of CH_2Cl_2 was added 1.00 g of trifluoromethanesulfonyl anhydride at −30 °C. After the mixture was stirred at −30 °C for 15 min, 0.2 mL of MeOH was added. The reaction mixture was concentrated in vacuo to give an oily residue, into which a solution of 325 mg of LiCl in 6 mL of DMF was added. After being stirred at ambient temperature for 30 min, the reaction mixture was poured into cold 1 N HCl and extracted with CH_2Cl_2. The extracts were washed with brine and dried over anhydrous $MgSO_4$. Filtration and concentration gave the crude product, which was chromatographed on silica gel. Recrystallization from EtOAc afforded 1.03 g of 13p (91% yield): mp 163–164 °C; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.19 (d, 6 H, J = 6.2 Hz), 1.35 (d, 3 H, J = 7.2 Hz), 1.53 (s, 3 H), 4.05 (s, 2 H), 4.39–4.46 (m, 1 H), 4.94 (q, 1 H, J = 6.2 Hz), 6.11 (s, 1 H), 6.33 (dd, 1 H, J = 10 Hz, J = 2.0 Hz), 6.18 (d, 1 H, J = 10 Hz); IR (KBr) 3450, 1735, 1660, 1620, 1610 cm^{-1}. Anal. ($C_{29}H_{39}ClFO_7$) C, H, Cl.

17α-((3-(*tert*-Butoxycarbonyl)propanoyl)oxy)-9α-fluoro-11β,21-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione (11q). Compound 11q was obtained by a procedure similar to that described for compound 11l. Betamethasone (1.00 g, 2.55 mmol) and the ortho ester 8q (1.61 g, 6.89 mmol) gave 10q, which was converted to 1.12 g of crude 11q. The crude 11q was used in the next step without further purification.

17α-((3-(*tert*-Butoxycarbonyl)propanoyl)oxy)-21-chloro-9α-fluoro-11β-hydroxy-16β-methylpregna-1,4-diene-3,20-dione (13q). Via the procedure for the preparation of 13p described above, 1.12 g of the crude 11q was treated with 0.81 g of trifluoromethanesulfonyl anhydride and 0.80 mL of pyridine in CH_2Cl_2 to give the crude triflate 12q, reaction of which with 0.38 g of LiCl in 7 mL of DMF gave, after purification by column chromatography on silica gel and recrystallization from EtOAc, 1.28 g of 13q (89% yield): mp 167–168 °C; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.35 (d, 3 H, J = 7.2 Hz), 1.40 (s, 9 H), 1.53 (s, 3 H), 4.06 (s, 2 H), 4.36–4.44 (m, 1 H), 6.11 (s, 1 H), 6.33 (dd, 1 H, J = 10 Hz, J = 2.0 Hz), 7.17 (d, 1 H, J = 10 Hz); IR (KBr) 3430, 1740, 1670, 1620 cm^{-1}. Anal. ($C_{30}H_{40}ClFO_7$) C, H, Cl.

21-Chloro-17α-((3-(ethoxycarbonyl)propanoyl)oxy)-9α-fluoro-11β-hydroxy-16β-methylpregna-1,4-diene-3,20-dione (13n). Into a solution of 0.50 g (0.95 mmol) of 13l in 25 mL of anhydrous EtOH was added a solution of 22 mg (0.95 mmol) of sodium in 25 mL of anhydrous EtOH. The reaction mixture was stirred at ambient temperature for 12 h. The resulting mixture was poured into cold water and extracted with EtOAc. The extracts were washed with brine and dried over anhydrous $MgSO_4$. Filtration and evaporation of solvents under reduced pressure gave the crude product, which was chromatographed on silica gel. Recrystallization from EtOAc and *n*-hexane afforded 0.29 g of 13n (57% yield): mp 228–230 °C; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.22 (t, 3 H, J = 7.0 Hz), 1.23 (d, 3 H, J = 8.0 Hz), 1.58 (s, 3 H), 4.08 (q, 2 H, J = 7.0 Hz), 4.33–4.52 (m, 1 H), 6.08 (s, 1 H), 6.26 (dd, 1 H, J = 10 Hz, J = 2.0 Hz), 7.21 (d, 1 H, J = 10 Hz); IR (KBr) 3450, 1735, 1705, 1665, 1610 cm^{-1}. Anal. ($C_{28}H_{38}ClFO_7$) C, H, Cl.

21-Chloro-9α-fluoro-11β-hydroxy-17α-((4-(methoxycarbonyl)butyryl)oxy)-16β-methylpregna-1,4-diene-3,17-dione (13m). Via the procedure for the preparation of 13n, 0.40 g (0.72 mmol) of 13o was treated with 39 mg (0.72 mmol) of NaOMe in 10 mL of anhydrous MeOH at room temperature for 12 h to afford, after purification by column chromatography and recrystallization from EtOAc and *n*-hexane, 0.24 g of 13m (62% yield): mp 251–254 °C; ^1H NMR ($CDCl_3$) δ 1.19 (d, 3 H, J = 7.6 Hz), 1.31 (s, 3 H), 1.57 (s, 3 H), 3.67 (s, 3 H), 4.35 (m, 1 H), 6.13 (s, 1 H), 6.33 (dd, 1 H, J = 10 Hz, J = 2.0 Hz), 7.21 (d, 1 H, J = 10 Hz); IR (KBr) 3450, 1740, 1700, 1660, 1610 cm^{-1}. Anal. ($C_{28}H_{38}ClFO_7$) C, H, Cl.

17α-((3-Carboxypropanoyl)oxy)-21-chloro-9α-fluoro-11β-hydroxy-16β-methylpregna-1,4-diene-3,20-dione (13r). Into a solution of 0.15 g (0.29 mmol) of 13l in 12 mL of AcOH was added 6 mL of 1 N HCl. After stirring was continued at 50 °C for 24 h, the resulting mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give, after column chromatography on silica gel, 0.14 g of 13r (92% yield) as an amorphous product: ^1H NMR ($CDCl_3$) δ 1.01 (s, 3 H), 1.38 (d, 3 H, J = 7.2 Hz), 1.56 (s, 3 H), 4.05 (s, 2 H), 4.43 (m, 1 H), 6.15 (s, 1 H), 6.37 (dd, 1 H, J = 10 Hz, J = 2.0 Hz), 7.22 (d, 1 H, J = 10 Hz); IR (KBr) 3425, 1730, 1655, 1610 cm^{-1}. Anal. ($C_{26}H_{32}ClFO_7$) C, H, Cl.

Croton Oil Induced Ear Edema in the Mice. The experimental procedure was conducted according to the method of Tonelli et al.[20] with some modifications. Male ddy mice 4 weeks old were used. The steroids in appropriate concentrations were mixed with an inflammatory vehicle consisting of 4 parts pyridine, 1 part 0.5% carboxymethyl cellulose in saline, 14 parts diethyl ether, and 1 part croton oil. The vehicle was applied to the right ear of unanesthetized mice by three uniform upward strokes of felt-tipped forceps. Five hours after the application, both ears were removed and weighed. The edema weight was obtained by subtracting the weight of the contralateral ear from that of the inflamed ear. For the purpose of estimating relative potency, the standard parallel line assay method was used.

Croton Oil Induced Granuloma Pouch in the Rats. The granuloma pouch test of Selye[21] was adopted with some modifications. The steroids in appropriate concentrations were mixed with an inflammatory vehicle consisting of 89 parts cotton seed oil, 10 parts ethanol, and 1 part croton oil. Male Wistar rats 6 weeks old were used. Each rat was lightly anesthetized with ether, and a pouch was produced by subcutaneously injecting 20 mL of air with a syringe in the middle of the back. Immediately, the inflammatory vehicle was injected into the pouch. Seven days later, the rats were weighed and killed. The pouch was carefully opened, and the inflammatory exudate present in the pouch was collected and the volume was measured. The granulation tissue, thymus, and adrenal glands were removed and weighed. For the purpose of estimating relative potency, the standard parallel line assay method was used.

Glucocorticoid Receptor Binding. The relative binding affinities of steroids for the glucocorticoid receptor of rat liver cytosol were measured by competitive displacement of [^{3}H]-dexamethasone. Male Wistar Imamichi rats 9 weeks old were used. Each rat was adrenalectomized under ether anesthesia. Two days later, the liver was excised and homogenized in a 10-fold buffer containing 50 mM Tris-HCl, 1 mM EDTA, 2 mM dithiothreitol, 10 mM Na_2MoO_4, and 10% glycerol (pH 7.4). The homogenate was collected as the supernatant fraction. The cytosol was centrifuged for 1 h at 105000*g* at 4 °C and collected as the supernatant fraction. The cytosol was mixed with 5 nM [^{3}H]-dexamethasone in the presence or absence of appropriate concentrations of competitors and incubated for 2 h at 4 °C. The reaction was terminated by the addition of hydroxyapatite in order to separate the receptor–steroid complex from free [^{3}H]dexamethasone. The radioactivity bound to the receptor was determined by liquid scintillation spectrometry. The IC_{50} values were estimated by probit analysis.

Registry No. 6a, 1738-36-9; 6b, 110-67-8; 6c, 107-14-2; 6d, 628-20-6; 6e, 5325-93-9; 6f, 35120-10-6; 6g, 109-77-3; 6h, 110-61-2; 6i, 5500-21-0; 6j, 6542-60-5; 6k, 105-34-0; 6l, 4107-62-4; 6o, 10444-38-9; 7a, 42945-65-3; 7b, 61737-87-9; 7c, 36743-68-5; 7d, 77570-15-1; 7e, 133871-47-3; 7f, 74979-21-8; 7g, 53557-70-3; 7h, 39547-14-3; 7i, 77570-14-0; 7j, 21572-78-1; 7k, 133871-48-4; 7l, 52070-12-9; 7o, 15687-71-7; 8a, 58995-66-7; 8b, 77197-59-2; 8c, 51076-95-0; 8d, 54917-75-8; 8e, 133871-49-5; 8f, 128788-71-6; 8g, 70138-31-7; 8h, 133871-50-8; 8i, 54917-76-9; 8j, 133871-51-9; 8k, 133871-52-0; 8l, 71235-00-2; 8o, 13464-27-2; 8p, 133871-53-1; 8q, 133871-54-2; 9, 378-44-9; 10l, 98040-72-3; 11l, 98008-92-6; 11p, 133871-55-3; 11q, 133871-56-4; 12l, 98008-94-7; 12q, 133871-57-5; 13a, 133871-58-6; 13b, 133871-59-7; 13c, 104449-53-8; 13d, 104449-40-3; 13e, 133871-60-0; 13f, 128420-94-0; 13h, 133871-61-1; 13i, 133871-62-2; 13j, 133871-63-3; 13l, 97342-63-7; 13m, 133871-64-4; 13n, 97342-80-8; 13o, 98009-01-9; 13p, 97342-82-0; 13q, 133871-65-5; 13r, 133871-66-6.

Supplementary Material Available: Tables of elemental analysis, NMR data, and IR data for 13 and NMR data for 8 (9 pages). Ordering information is given on any current masthead page.

(21) Selye, H. *Rec. Prog. Horm. Res.* **1953**, *8*, 117.

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